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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,005	09/11/2000	Erich Wanker	V0179/7001	1379

7590 12/11/2006

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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,005	WANKER ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-20 and 27-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13-16 and 31-41* is/are allowed.

6)☒ Claim(s) *1-5,8-12,17-20 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed on September 21, 2006 is acknowledged and has been entered. Claims 1, 8-11 and 13 have been amended. Claim 7 has been cancelled. Accordingly, claims 1-5, 8-20, and 27-41 are pending and are under examination.

Withdrawn Rejections

2. All rejections not reiterated herein, have been withdrawn

3. The rejections of claim 7 are now moot in light of Applicant's cancellation of the claim.

4. In light of Applicant's amendment, the rejection of claims 1-5, 8-12, 18-20, and 27 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 10, 12, and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Notario et al. (Changes in the membrane proteins of blood cells in the course of embryonal megaloerythropoiesis in relation to hemoglobin maturation) Archivio per le scienze mediche, 135 (1): 1-8 (1978 Jan-Mar) Abstract) in view of Mueller (US Patent 4,094,775) or Gokcen (US Patent 6,428,785).

Notario et al. teach contacting a sample material (circulating blood cells) having membrane proteins, with cellulose acetate for determination of hemoglobin electrophoresis patterns and detection of the protein aggregates inherently present in the membrane proteins on the cellulose acetate membrane, after solubilization by urea or detergent, sodium dodecyl sulphate (SDS) (see Abstract).

Notario et al. differs from the instant invention in failing to teach using cellulose acetate membrane as filter for capturing the urea or detergent insoluble protein aggregates.

Mueller discloses that cellulose acetate membrane filters are used in filtration methods for capturing or retaining (preventing passage of) very large protein molecules and cellular constituents (see column 4, lines 27-37).

Gokcen discloses that cellulose acetate and polysulfone membrane filters are low protein binding filter membranes used in filtration methods for capturing or retaining insoluble particulates, i.e. protein, and micro aggregates (see column 10, lines 23-28).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used the cellulose acetate membrane in the method of Notario as a filter for use in capturing and retaining the urea insoluble protein aggregates in a filtration process as taught by Mueller or Gokcen, because both of Mueller and Gokcen specifically provided that cellulose acetate membranes are known for their low adsorption or protein binding capability and are conventionally and advantageously used for separating, capturing, and isolating large insoluble protein molecules in membrane filters.

6. Claims 2-5, 8, 9, 11, 17, and 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Notario et al. (Archivio per le scienze mediche, 135 (1): 1-8 (1978 Jan-Mar) Abstract) in view of Mueller (US Patent 4,094,775) or Gokcen (US Patent 6,428,785), as applied to claims 1, 10, 12, and 18-20 above, and in further view of Kalchman et al. (WO 97/18825).

Notario et al., Mueller, and Gokcen are discussed supra.

Notario, Mueller, and Gokcen differ from the instant invention in failing to teach identifying the captured protein aggregates or amyloid-like fibrils that are retained in the cellulose acetate filter.

Kalchman et al. provide that the interaction between HD proteins and HIP1 is influenced by the number of polyglutamine repeats and that expanded polyglutamine tracts aggregate into large irregularly shaped deposits in brains of Huntington disease (see pages 1, 6, and 7). Kalchman et al. provide that individuals suffering from Huntington's disease have polyglutamine expansions of at least 35 glutamines, at least 41 glutamines, at least 48 glutamines, or at least 51 glutamines, (36 or greater glutamines) (see page 2). Kalchman et al. also found that HIP1 protein is insoluble to treatment with Triton X-100 (see Examples 7 and 8). In practice, proteins from tissues and cells of human and other mammals are solubilized with detergent, and spotted or dotted (electroblotted) on SDS-PAGE mini-gels so as to provide detection of HIP1 and huntingtin proteins. Immunoreactivity is determined using antibodies against HIP1 and Huntingtin and visualized in chemiluminescent ECL solution.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have incorporated cellulose membrane filters as taught by Notario and modified by Mueller or Gokcen for use in capturing and isolating large insoluble proteins or amyloid-like fibrils, such as HIP1 that are sought to be detected in the method of Kalchman, because Mueller and Gokcen specifically provided that cellulose acetate membranes are known and conventionally used as filters in filtering, capturing, and retaining sample materials having large insoluble protein molecules and are

recognized for their advantage of having low adsorption or protein binding capability, which render them useful in isolation methods for separating large insoluble protein aggregates such as the HIP1 and huntingtin proteins in the method of Kalchman, for purposes of determining and identifying their presence in a sample as markers for indication of a particular disease such as those associated with polyglutamine repeats.

Response to Arguments

7. Applicant's arguments filed on September 21, 2006 have been fully considered but they are not persuasive.

Applicant argues that the requirements for a prima facie case of obviousness have not been met in combining the three references as cited by the Examiner because there is no motivation to combine the teachings in the references to make the claimed invention, there is no reasonable expectation of success in making the combination, and that the references do not teach every element of the claimed invention.

A) Applicant specifically argues that Examiner's interpretation of the Notario Abstract is flawed because Notario only describes routine electrophoretic separation of proteins along a cellulose acetate membrane, which is not a method of filtering insoluble from soluble proteins in a solubilized sample. Notario does not teach a method of solubilizing a solution that includes proteins and filtering the solution through a filter to retain insoluble proteins and to allow passage of soluble proteins.

In response to applicant's arguments against the Notario reference individually, one cannot show nonobviousness by attacking references individually where the

rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Notario is cited for teaching a method wherein a sample material of circulating blood cells having membrane proteins which are previously treated with urea or detergent, sodium dodecyl sulphate (SDS), is contacted with cellulose acetate membrane for determination of hemoglobin electrophoresis patterns and detection of the protein aggregates inherently present in the membrane proteins on the cellulose acetate membrane (see Abstract). Mueller and Gokcen were combined with Notario for teaching use of cellulose acetate membrane as a filter for filtering a sample to capture or retain large protein molecules or protein aggregates. Mueller discloses that cellulose acetate membrane filters are used in filtration methods for capturing or retaining very large protein molecules. Gokcen also discloses that cellulose acetate filters are low protein binding filter membranes used in filtration methods for capturing or retaining large insoluble protein aggregates. The result of the combination of these references appears to provide the claimed invention because it appears to teach each and every element of the claimed invention. Additionally, Mueller and Gokcen provide motivation to use the cellulose acetate membrane taught by Notario as a filter, for its conventional and advantageous use in capturing insoluble protein aggregates from a sample material previously treated with urea of detergent, wherein the insoluble protein aggregates would appear to be inherently large proteins that are captured during the filtration process.

B) Applicant argues that the examiner's interpretation of the Mueller reference is also flawed because Mueller only discloses that the cellulose acetate filter does not allow passage of very large molecules such as proteins and cellular constituents of the blood. Applicant submits that Mueller does not teach or suggest use of the filter to separate insoluble from soluble proteins, as claimed.

In response to applicant's arguments against the Mueller reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Mueller was combined with Notario for teaching use of cellulose acetate membrane as a filter for filtering a sample to capture or retain large protein molecules or protein aggregates. Mueller specifically discloses that cellulose acetate membrane filters are used in filtration methods for capturing or retaining very large protein molecules. Notario is cited as primary reference for teaching a method wherein the sample material having membrane proteins which are previously treated with urea or detergent, sodium dodecyl sulphate (SDS), is contacted with cellulose acetate membrane for determination of hemoglobin electrophoresis patterns and detection of the insoluble protein aggregates inherently present in the membrane proteins on the cellulose acetate membrane. The result of the combination of these references appears to provide the claimed invention because it appears to teach each and every element recited in the claims. In addition, the issue of insoluble proteins being captured in the filter versus soluble proteins (as claimed), and large protein

aggregates being captured in the filter versus smaller proteins (as taught in Mueller), both encompass the issue of size of the protein as being large. Insoluble proteins that are not solubilized are inherently large proteins and hence, are captured and not filtered through. Absent evidence to the contrary, the insoluble proteins in the claimed invention are inherently large proteins or protein aggregates; hence are captured by the cellulose acetate filter, the concept of which is consonant with the teaching of Mueller.

C) Applicant argues that the examiner's interpretation of the Gokcen reference is also flawed because Gokcen only discloses filtering to sterilize a pharmaceutical solution to minimize risk to patients posed by insoluble particulates or micro aggregates. Applicant submits that Gokcen does not teach or suggest use of the filter to separate insoluble from soluble proteins, as claimed.

In response to applicant's arguments against the Gokcen reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Gokcen was combined with Notario for teaching use of cellulose acetate membrane as a low protein binding filter membrane for use in filtering a sample to capture or retain insoluble particulates or protein micro aggregates. Notario is cited as primary reference for teaching a method wherein the sample material having membrane proteins which are previously treated with urea or detergent, sodium dodecyl sulphate (SDS), is contacted with cellulose acetate membrane for determination of

hemoglobin electrophoresis patterns and detection of the insoluble protein aggregates inherently present in the membrane proteins on the cellulose acetate membrane. The result of the combination of these references appears to provide the claimed invention because it appears to teach each and every element of the recited claims. In addition, the issue of insoluble particulates and protein micro aggregates being captured versus soluble proteins (as claimed), and large protein micro aggregates being captured versus smaller particulates (as taught in Gokcen), both encompass the issue of size of the protein aggregates as being large. Insoluble particulates and proteins that are not solubilized are inherently large and hence, are captured and not filtered through. Absent evidence to the contrary, the insoluble protein aggregates in the claimed invention are inherently large proteins or protein aggregates; hence are captured by the cellulose acetate filter, the concept of which is consonant with the teaching of Gokcen.

D) Applicant argues that the combination of Kalchman with the teachings of Notario as modified by Mueller and Gokcen does not suggest or render obvious the claimed invention. Applicant specifically contends that contrary to Examiner's cited Office Action on the Kalchman reference, Kalchman does not teach or suggest use of a filter device or a filtration method to separate insoluble proteins from soluble proteins, but rather describes use of electrophoretic methods to separate insoluble proteins (HD1 and huntingtin) from each other followed by blotting of the separated proteins onto a PVDF membrane for detection of the proteins in separated locations of the membrane.

In response to applicant's arguments against the Kalchman reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Kalchman was combined with Notario, Mueller, and Gokcen (discussed supra) for teaching that interaction between HD proteins and HIP1 is influenced by the number of polyglutamine repeats and that expanded polyglutamine tracts aggregate into large irregularly shaped deposits in brains of Huntington disease. Kalchman teaches that HIP1 protein is specifically insoluble to treatment with detergent Triton X-100, and that after solubilization with detergent, is spotted or dotted (electroblotted) on SDS-PAGE mini-gels so as to provide a determination of the presence of HIP1 and huntingtin proteins using antibodies against HIP1 and Huntingtin. Contrary to Applicant's argument, Examiner's last Office Action does not rely on Kalchman for teaching a filtering device or a filtering method, since Mueller and Gokcen were relied upon in the cited combination for such teaching. See discussion of Notario, Mueller, and Gokcen supra.

In response to Applicant's argument that there is no suggestion or motivation or reasonable expectation of success in combining the references as cited, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*,

837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, claim 1 simply recites that a sample suspected of having amyloid-like fibrils or protein aggregates is treated with detergent or urea for subsequent contact with cellulose acetate for detection of protein aggregates inherently present in the sample (Notario provides this teaching), then the sample is contacted with a cellulose acetate membrane filter used as filtration device to capture those urea or detergent insoluble amyloid-like fibrils or proteins aggregates which are not solubilized; hence, remain as insolubilized large proteins or aggregates (Mueller or Gokcen provide this teaching and motivation to use cellulose acetate membrane filter in filtration methods for separating large protein aggregates), and then the presence of [insoluble] amyloid-like fibrils or aggregates that are not solubilized by detergent Triton X-100 and that would have been retained on the filter such as those associated with polyglutamine expansion as claimed, are detected using antibodies specific thereto (Kalchman provides this teaching). Accordingly, the combination of Notario with Mueller or Gokcen, and further in view of Kalchman, appears to render obvious the claimed invention.

Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

Allowable Subject Matter

8. Claims 13-16 and 31-41 are clear of the prior art of record. The prior art of record fails to teach or fairly suggest filtering and capturing detergent- or urea-insoluble amyloid-like fibrils or protein aggregates on low capacity protein adsorption filter and detecting the presence or concentration thereof, wherein the captured amyloid-like fibril or protein aggregate is a fusion protein comprising 1) a polypeptide that enhances solubility or prevents aggregation of the fusion protein; 2) an amyloidogenic polypeptide that self assembles into amyloid-like fibrils or protein aggregates when released from the fusion protein; and 3) a cleavable site that separates 1) and 2) of the fusion protein; and wherein prior to capturing and detecting for the fusion protein, the sample is incubated with a suspected inhibitor of amyloid-like fibrils and protein aggregate formation, and simultaneously or concurrently, the sample is further incubated with a compound that induces cleavage at the cleavage site that separates the components of the fusion protein. The object of using low capacity protein adsorption filter is to capture only detergent- and urea- insoluble amyloid-like fibrils and protein aggregates in the filter membrane for detection, and to ensure filtration of solubilized fibrils and proteins through the membrane filter for purposes of exclusion thereof, into solution.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gailene R. Gabel
Patent Examiner
Art Unit 1641
December 6, 2006